REMARKS

Claims 1, 2, 5, 9 and 10 have been amended to set forth the phenotype of the mouse. The Examiner has stated that this phenotype is enabled by the specification. Claim 6 has been amended to specify that the elastase is purified elastase, the elastase activity is measured and compared in the presence and absence of a drug and that any drug which inhibits elastase activity is a candidate drug which may be useful for treating or preventing the specified conditions. It is believed that these amendments do not constiute new matter, and their entry is requested.

The Examiner rejected claim 6 under 35 U.S.C. § 112, second paragraph for being indefinite. It is believed that the insertion of the term "purified" with respect to elastase makes it clear that the activity of the enzyme is measured in the presence and absence of a drug candidate. The elastase activities in the presence and absence of a drug candidate are then compared. Thus, it is submitted that claim 6 fully sets forth the method for screening for drug candidates and is not indefinite. Withdrawal of this rejection is requested.

The Examiner rejected claims 1, 2, 5, 6, 9 and 10 under 35 U.S.C. § 112, first paragraph for lack of enablement. It is believed that the amendment of claims 1, 2, 5, 9 and 10 to set forth the enabled phenotype obviates the rejection with respect to these claims.

Claim 6 has been amended to more clearly indicate that what is being claimed is a screening method which allows one to screen for drug candidates which **may be** useful in treating or preventing atherosclerosis, SVAS or essential hypertension in humans. It is meant as an initial screening method to narrow the number of drug candidates. Claim 6 is drawn to a method which is clearly a screening mechanism, effectively a first screen to narrow the number of drug candidates. It is unlikely that every drug candidate identified in this screen will be a useful drug, only that it is a candidate which may be a useful drug. Potential drugs which have no inhibitory effect on elastase will be discarded as candidates, whereas those which do have an effect will be used in more definitive tests.

In view of the amendments to the claims and the above arguments, it is urged that claims 1, 2, 5, 6, 9 and 10 are enabled, and it is requested that the rejection of these claims under 35 U.S.C. § 112, first paragraph be withdrawn.

The Examiner rejected claims 1-4 under 35 U.S.C. § 103 as being unpatentable over Sechler et al. (1995) in view of Morris (1998) and Wydner et al. (1994). This rejection is similar to a previous rejection except that the Morris reference has been added. Applicants submit that the present invention was made prior to the publication date of the Morris reference. Therefore, Applicants submit that Morris is not prior art with respect to the present invention. Applicants are in the process of preparing a suitable Rule 131 Declaration for swearing behind the Morris reference. This Declaration will be submitted as soon as it has been executed by the inventors and received by the undersigned.

Since Morris is not prior art with respect to the present invention, Applicants submit that the presently claimed invention is not obvious over Sechler et al. in view of Wydner et al. for the reasons previously provided. Specifically, Applicants urge that at best the combination of the cited references would motivate one of skill in the art to make mice which are transgenic for a **mutated** mouse elastin gene but which also comprise normal wild-type mouse elastin genes. The mice of the Sechler et al. reference comprise not only the transgenic mutant rat elastin gene but also comprise the normal wild-type mouse elastin genes which are still active. This is seen in several places in the reference. The first paragraph of the Results and discussion section on page 150 of the Sechler et al. reference states that the reasoning behind the construction of the mice was to produce mice which would synthesize a mutated elastin which would be incorporated into the elastin matrix together with the normal, endogenous mouse elastin. This clearly establishes the motivation of producing the mice - to study animals making a combination of both mutant and wild-type elastin. Data showing that the mice studied for the publication did in fact produce both types of elastin is shown, e.g., in Table 1 on page 153 of the Sechler et al. publication. Both rat and mouse tropoelastin mRNA were produced with the levels of endogenous mouse tropoelastin mRNA set at a value of 100% and the rat levels based on a comparison to that value. The middle of the last paragraph on page 14 of the publication states that levels of expression of the rat transgenes in skin was usually comparable to or exceeded that of the endogenous expression of the mouse gene. Table 2 on page 158 of the Sechler et al. publication shows that both the rat and mouse elastin proteins were being synthesized in the transgenic animals.

The claims which are pending are not drawn to mice or mouse cells comprising a **mutated** gene plus a wild-type gene, rather the claims are drawn to mice or cells which have a) a single functional elastin gene or ii) no elastin gene. This difference is critical. The claimed mice and cells are ones which end up being **deficient** in elastin rather than comprising some type of **mutated** elastin. Mice (and humans) which are deficient in elastin have different medical conditions than those which synthesize a mutated elastin.

It is submitted that the present claims do not encompass elastin genes which are transcribed but are nonfunctional because of a mutation which is present, rather they encompass the presence of only at most a single elastin gene which produces an elastin protein which can be incorporated into a matrix. It is urged that the claim language clearly distinguishes the claims from the prior art and prevents the claims from being read broadly enough to be encompassed by or made obvious by the prior art. No prior art reference has been cited that teaches a mouse or mouse cell comprising no or only one elastin gene, which will be transcribed into RNA that will be translated into a protein which can be incorporated into the extracellular matrix.

Applicants urge that there is a crucial difference between the prior art and the claimed invention. The prior art teaches medical problems which are associated with the presence of a **mutated** elastin, not with a **deficiency** of elastin. The Sechler et al. reference teaches on pages 162-163 that disruptions in the region of the elastin gene are associated with SVAS. In fact, this teaching states that it was not known if the disruption of the elastin gene causes the SVAS phenotype or whether the defect results from a disruption of another gene near the elastin gene (see the final sentence on page 162 continuing onto page 163). Based on this fact alone, it is urged that at best there would be merely an "obvious to try" motivation to produce mice with mutated elastin genes and the usefulness of such mice would not be "obvious". This alone should be enough to overcome the "obviousness" rejection. However, applicants urge that there are even more reasons that the obviousness rejection is improper. If one were to accept that the references teach that mutations in elastin actually do result in SVAS, the Sechler et al. reference teaches that these mutations involve a breakpoint near the 3' end of the tropoelastin gene (see the final paragraph on page 162). This means that a somewhat truncated version of elastin is produced and it is this truncated version which

causes SVAS. The Sechler et al. reference teaches that there is support for the idea that incorporation of the truncated elastin into fibers results in SVAS (see page 163). Therefore to study SVAS one would be motivated to produce **mutated** elastin such that a mutant form of elastin would be produced and be inserted into fibers to produce aberrant fibers. That is exactly what Sechler et al. did and that is what their results support, i.e., they prepared mice which produced mutated forms of elastin. Sechler et al. produced no mice which were deficient in elastin, rather their mice produced normal amounts of wild-type elastin plus a mutated form of elastin which interacted with wild-type elastin in forming aberrant fibers and produced mice which have fiber morphology similar to SVAS (see page 163). These results would point one in the direction of studying mutated forms of elastin rather than gene dosage effects. It is urged that no references have been pointed to which disclose any studies on mice which are deficient in elastin, rather the prior art teaches that conditions such as SVAS are likely caused by mutated forms of elastin being incorporated into fibers thereby producing aberrant fibers. This would not lead one to conclude that a mouse producing a deficient amount of solely wild-type elastin would produce aberrant fibers since only wild-type elastin would be present. The results disclosed in the present application teach otherwise, but such studies were never reported in the prior art. The medical condition which results from a lack of elastin is different from that seen due to the presence of a mutated elastin. Mutated elastin leads to aberrant elastic fibers whereas a lack of elastin results in proliferation of smooth muscle and contributes to obstructive arterial disease (see Summary of the Invention on pages 2-3 of the application). It is urged that the prior art would lead one only to study mice with mutated forms of elastin, not to study mice with solely a deficiency of wild-type elastin.

In view of the above remarks, it is believed that claims 1-4 are not rendered obvious by the cited prior art. Withdrawal of this rejection is requested.

The Examiner has rejected claims 5, 9 and 10 under 35 USC §103(a) as being unpatentable over Reitamo et al. (1994) in view of Sechler et al., Morris and Wydner et al. Since, as discussed above, Morris is not prior art with respect to the present invention. Since Morris is not prior art, Applicants submit that the presently claimed invention is not obvious over Sechler et al. in view of Wydner et al. for the reasons previously provided. Specifically, Claims 5, 9 and 10 are directed to

mice or humans or their cells which are *ELN* +/- with the further requirement that these organisms or cells comprise only one functional elastin gene and either no second elastin gene or an elastin gene with a null mutation. It is urged that these amendments prevent the claims from being read to encompass the use of organisms or cells which comprise one wild-type elastin gene plus one mutated elastin gene wherein the mutated elastin gene results in the synthesis of a mutated elastin which can be incorporated into extracellular matrix. It is urged that the cited prior art neither teaches nor suggests a mouse or human with only a single elastin gene which produces elastin which will be incorporated into extracellular matrix or using such organisms or cells for drug screening for drugs which will be useful for treating atherosclerosis, SVAS or hypertension. The arguments set forth above concerning the fact that the prior art would lead one only to study animals with mutated versions of elastin and not animals which are deficient in elastin apply to claims 5, 9 and 10 which require the use of animals which are deficient in elastin.

In view of the above remarks, it is believed that claims 5, 9 and 10 are not rendered obvious by the cited prior art. Withdrawal of this rejection is requested.

In view of the amendments and above arguments, it is submitted that the present claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application.

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Attachments: Marked-Up Copy of Amendments

Amended Claims: Version with markings to show changes made

1 (four times amended). A mouse comprising a genome comprising a) exactly one functional elastin gene and b) either one mouse elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae and arterial occlusion.

2 (amended). A mouse comprising a genome with no functional elastin gene, wherein said mouse has an increased number of elastic lamellae and arterial occlusion.

5 (three times amended). A method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis or useful for preventing atherosclerosis in humans, said method comprising administering said drugs to an *ELN* +/- mouse or human, wherein said *ELN* +/- mouse or human comprises a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae and arterial occlusion, wherein drugs which inhibit occlusion of arteries in said organism are said drug candidates.

6 (twice amended). A method to screen for drug candidates which may be useful for (i) treating humans with atherosclerosis, SVAS or essential hypertension or (ii) preventing the occurrence of atherosclerosis in humans said method comprising measuring activity of purified elastase in the presence and absence of [drugs] a drug and comparing the elastase activity in the presence and absence of said drug, wherein [said drugs] a drug which inhibit elastase [are said drug candidates] is a drug candidate which may be useful for (i) treating humans with atherosclerosis, SVAS or essential hypertension or (ii) preventing the occurrence of atherosclerosis in humans.

9 (three times amended). A method to screen for a drug candidate useful for treating atherosclerosis, hypertension or SVAS in a human, said method comprising treating an *ELN* +/- mouse or human or *ELN* +/- mouse or human cells, wherein said *ELN* +/- mouse or human or mouse

or human cells comprise a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae and arterial occlusion, with drugs and measuring synthesis of elastin RNA wherein a drug which increases synthesis of elastin RNA in said organisms or in said cells is said drug candidate.

10 (twice amended). A method to screen for a drug candidate useful for treating atherosclerosis, hypertension or SVAS in a human, said method comprising treating *ELN* +/- mice or *ELN* +/- mouse cells, wherein said *ELN* +/- mice or mouse cells comprise a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae and arterial occlusion, with drugs and measuring synthesis of elastin wherein a drug which increases synthesis of elastin is said drug candidate.